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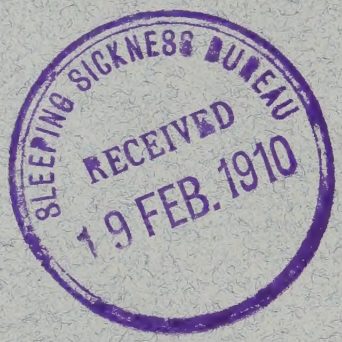
The Milroy Lectures

ON KALA-AZAR

(ABSTRACTS)

DELIVERED BEFORE THE ROYAL COLLEGE OF PHYSICIANS OF LONDON.



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BY

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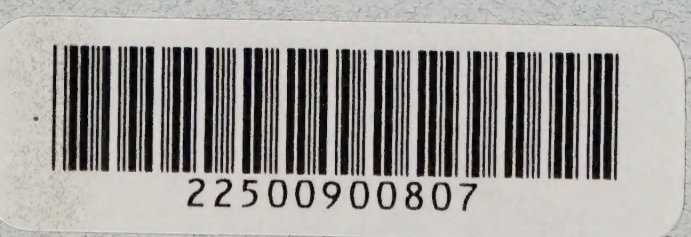

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LECTURE I.

THE ORIGIN AND COURSE OF THE EPIDEMIC.

I REGARD my good fortune in being appointed to deliver the Milroy Lecture this year as being due to a desire on the part of this College to recognize the work now being done in the investigation of tropical diseases. As my subject is one which must be unfamiliar to most of my audience, I will commence with an extended definition of the disease, embracing the main points I shall have to deal with much in the order in which they will be taken up.

Kala-azar, then, is the epidemic manifestation of a fever, endemic in extensive areas of India, which has spread slowly for thirty years up the Assam valley as a wave of greatly-increased mortality, dying out largely as it passes on, after causing a decrease in the population of the affected tracts and the falling out of cultivation of much land, travelling along lines of communication, and checked by high elevations and extensive areas of unpopulated jungle, and now happily largely on the decrease. It is precisely similar in nature to a previous epidemic in Bengal known as "Burdwan fever." Cases of the epidemic disease, individually considered, are identical with the sporadic form known for centuries as "malarial cachexia," and is characterized by very persistent fever, of an alternating, remittent, and intermittent type, commonly mistaken for typhoid in the earlier remittent stage, but rapidly leading to a cachectic condition, with great enlargement of the spleen and later of the liver, and extreme wasting, the fever lasting from a few months to several years, and commonly terminated by some complicating affection; the mortality being from 98 per cent. at the height of the epidemic down to 75 per cent. at its end. The disease in its progressive stages is constantly associated with, and pretty certainly caused by, a minute protozoal organism, which has been shown by a remarkable cultivation outside the human body to be one stage of a flagellated parasite, while a study of the conditions

most favourable to this development of its extracorporeal stage strongly indicate some biting insect as the carrier of the infection—a view which is also in accordance with a number of facts regarding the spread of the disease and the success which has attended efforts to check its further extension and to stamp it out of infected places, made before the discovery of the parasite, and also recently confirmed by certain feeding experiments.

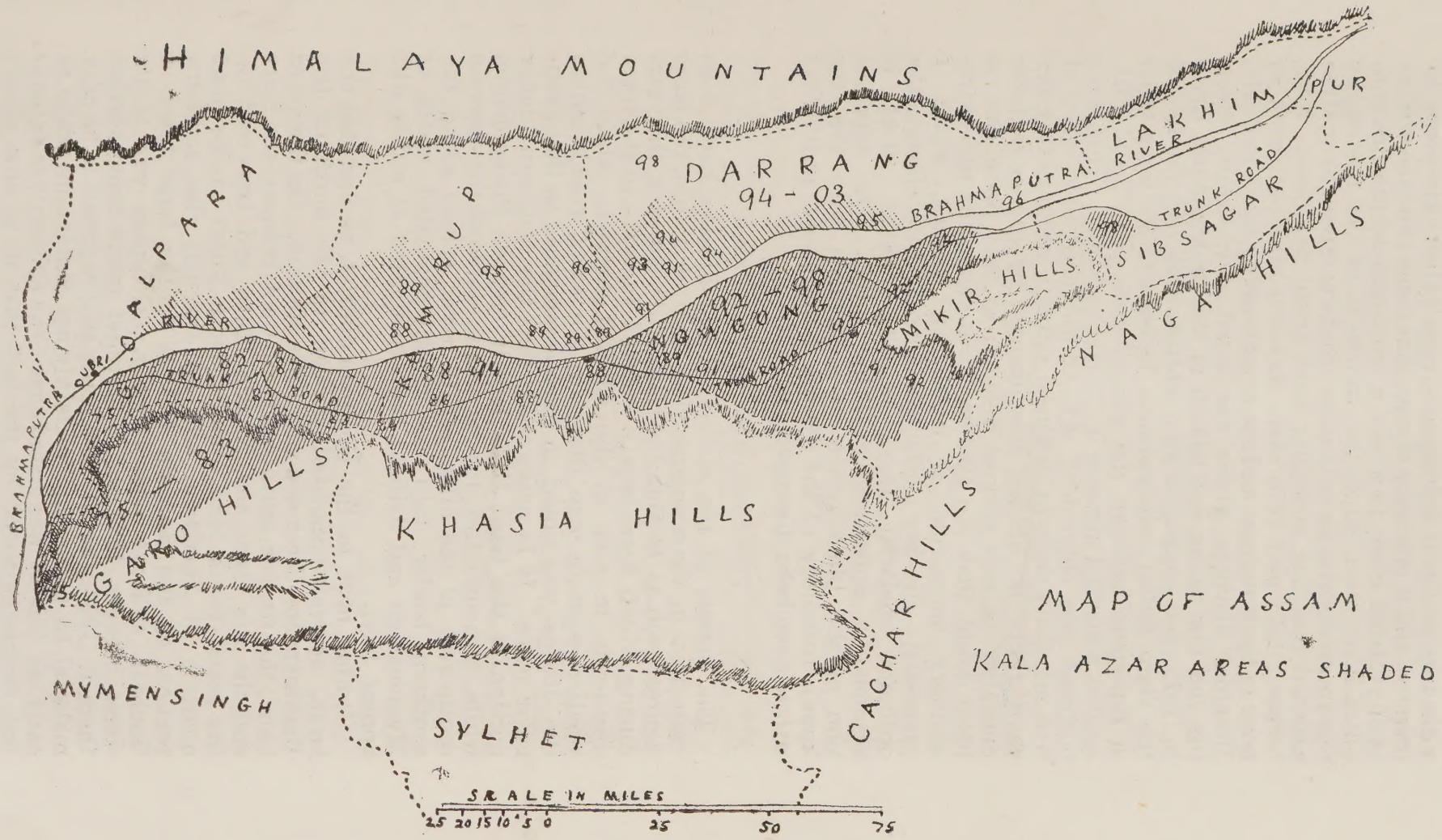
To-day I propose to deal solely with the subject in its epidemiological aspect; taking it up as a disease, individually considered, in the second; and describing the life-history of the parasite and its bearing on the mode of infection in my third lecture.

The Origin of the Epidemic.

Kala-azar first attracted public attention in 1882, when Dr. Clarke, the Sanitary Commissioner with the Government of Assam, in his annual report, gave an account of the disease based on the notes of 120 cases compiled by Mr. McNaught, the Civil Medical Officer of the Garo Hills. He described it as a very severe form of malarial cachexia, which was depopulating certain areas at the foot of the Garo Hills, and believed by the Garos to be infectious, and obtaining its name from a peculiar dusky hue which the sufferers presented, the term meaning "black fever." The disease had been known there in its sporadic form since 1869, when the country was occupied by the British, but the exact date of origin of the epidemic was obscure when I went to Assam in 1896. I therefore visited the Garo Hills to examine all the medical and administrative records, and ascertained that the Government land rent was paid in full up to 1875, when it was recorded that a deficiency occurred in some of the villages at the south-west corner of the district owing to several families having died of kala-azar, and from this time onwards it was regularly referred to year by year as causing the deaths of a large proportion of the people of various villages, thus occasioning a loss of revenue and depopulating certain areas at the foot of the hills just to the east of the Brahmaputra River. In 1881 numerous villages had quite disappeared, and the epidemic travelled towards the centre of the hills, and then by a bridle path out again to the foot of the hills on the north side to reach Damra, in the south of the Goalpara district. It is clear, then, that although the disease had doubtless long been present in a sporadic form at the western foot of the Garo Hills, just as it is known to have been in the Rungpore district on the west of the Brahmaputra River, yet it was not until 1875 that it assumed the epidemic spreading form, depopulating tracts of country, and immediately causing a marked loss of revenue—characteristics which it maintained during its subsequent spread up the Assam Valley during the succeeding three decades.

Moreover, about 1875, the disease also appeared in an epidemic form in a village to the south of Dubri, some fifty miles north of the above-mentioned place of origin,

DIAGRAM I.


HIMALAYA MOUNTAINS
GOALPARA
DARRANG
94 - 03
BRAHMAPUTRA RIVER
LAKHIMPUR
TRUNK ROAD
SIBSAGAR
NAGA HILLS
MIKIR HILLS
RIVER
TRUNK ROAD
GARO HILLS
KHASIA HILLS
CACHAR HILLS
MYMENSINGH
SYLHET
SCALE IN MILES
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MAP OF ASSAM
KALA AZAR AREAS SHADED

a distance which it subsequently took about five years to traverse, and it is worthy of note that these two places were each situated close to where a ferry crossed the Brahmaputra River from Rungpore; while in two of the earlier reports on the disease it is stated that the Garos themselves asserted that the epidemic came from Rungpore. Now, between 1871 and 1876 there was a terrible outbreak of fever in the Rungpore and the neighbouring, more westerly, Dinajpur districts, which was noted as especially affecting the low banks and islands of the Brahmaputra River in 1875 (and consequently doubtless involving the foot of the Garo Hills), and causing a decrease in the population of Rungpore between the two censuses of 1872 and 1881, against a marked increase in Bengal generally. This fever outbreak was coincident with an unprecedented series of five out of six years of deficient rainfall, while to this day short rains are always accompanied by excessive fever mortality in this part of Bengal ; so that there can be little doubt that the epidemic was caused by this extraordinary succession of unhealthy seasons, which I suggested in my original report intensified the ordinary malarial fever of the district until it assumed a spreading epidemic form. The explanation of the phenomenon in accordance with the now known pathology of the disease I must leave until other points have been discussed.

The Spread of the Epidemic.

The details of the spread of the disease have been embodied in the accompanying map of Assam, the large figures, such as 75-83 in the Garo Hills, showing the years during which there was a marked increase in the fever death-rate in each of the affected districts, while the smaller separate ones illustrate the exact year in which the disease was noted to have commenced in that particular place. It is noteworthy that the southern higher portion of the Garo Hills largely escaped the epidemic, while, although the disease first appeared at the extreme south-west of the hills, yet it never spread along the southern border into the thickly-populated tracts of Mymensingh and Sylhet ; the explanation of which will appear later.

Coming next to the Goalpara district, we find that the large, sparsely-populated portion to the north of the Brahmaputra River was very little affected. On the other hand, the narrow southern Terai tract between the river and the low Garo and Khasia Hills, and traversed by the grand trunk road from opposite Dubri to the head quarters of Goalpara, and on through the southern portion of the Kamrup district to the large town of Gauhati, suffered very severely. Goalpara was at its worst between 1882 and 1887, relief works being started there in 1884, the disease being still reported to be only malarial in nature and certainly not contagious, while as early as this it was stated that " the epidemic is extending, counterbalanced by the fact that it is now absent

where it has been severe." Moreover, in 1886 it was recorded of a tract of the Garo Hills some seventy miles in extent, which had suffered most severely from the disease, "It would be hard to find one single case of the real disease, kala-azar." It is clear from this that the decline of the epidemic is just as marked a feature as its rapid rise in any district.

In the meanwhile the southern part of Kamrup was invaded, and some of the villages on the north bank of the great river gradually became infected, about ten miles of new country being invaded each year where communications were good, while the disease leapt on into the town of Gauhati in 1888 in accordance with the more active intercourse between that place and the infected villages, than with some of the intervening and later affected hamlets. On the north bank the spread was less rapid, on account of the slighter active communication between the more scattered villages of that tract, there being no much-frequented main road through it. Once Gauhati became severely infected, the disease spread across the river by a main road into the westerly Mangaldai subdivision of the Darrang district, and at the same time it continued its steady eastward course along the trunk road into the Nowgong district, leaping on once more into the town of that name in 1890.

In the meantime attention had been called in Ceylon to the amount of anaemia produced in coolies by the *Ankylostoma duodenale*, and Dr. Ruddock had also found ankylostomiasis to be common in Assam, where it was readily cured by thymol. Dr. Giles, I.M.S., was therefore sent to Assam late in 1889 to investigate both kala-azar and anaemia of coolies, and rapidly came to the conclusion that they were one and the same disease, and caused by the ankylostomes, and he reported to this effect in 1890. He found, indeed, that many of the cases showed symptoms of malarial poisoning, but as enlarged spleen was very common in healthy people in Assam, he considered that "it is obviously absurd to attach any pathognomonic importance to the symptom in connexion with the etiology of kala-azar," and after studying anaemia of coolies in the eastern part of the valley—where there has never been any kala-azar to the present day—he wrote: "Nothing here struck me so strongly as the absolute identity of the clinical pictures presented by these cases of acknowledged ankylostomiasis with those I had been seeing so much of under the name of kala-azar," and he concluded that, although malaria causes much death-rate in Assam, there had been no change in the country which could intensify it, and "it is entirely inadequate to serve as the efficient cause of the terrible death-rate of kala-azar stricken villages, and the true cause of this will be found to be neither more nor less than ankylostomiasis." This identity of clinical pictures can only be explained by Dr. Giles having rejected typical cases of kala-azar as being merely "the common malarial cachexia of Assam," and only regarded cases of ankylostomiasis as

the true cause of the increased mortality, that is, kala-azar as he saw it. Unfortunately he did not examine the healthy people for the intestinal parasite, so when soon after Dr. Dobson showed that 80 per cent. of healthy coolies imported from various parts of India, and who had passed two medical examinations, harboured this worm, Dr. Giles's theory received a fatal blow, and in 1896, a fresh investigation was ordered, which I was fortunate enough to be selected to carry out.

In the course of a year's study I found that ankylostomes were no more common in any stage of kala-azar than in the uninfected people, while the anaemia produced by this worm was of the chlorotic type, thus differing so widely from the pernicious form met with in kala-azar as to alone serve for the complete differentiation of the two diseases, which finally disproved Dr. Giles's theory. Moreover, I found malarial parasites frequently present in all stages of the disease—a complication now easily explained by the then unknown fact that in very malarious places a larger proportion of the healthy persons show malarial parasites in their blood, for on revisiting the Nowgong district in 1904 I found the endemic index, or percentage of healthy children with malarial parasites in their blood, no less than 80 on some of the very tea gardens where I had studied kala-azar in 1896. Further, I was unable to find any differences between kala-azar and malarial fever in any stage; malarial pigment was almost constantly found in the organs after death, while the typical cachectic later stage of kala-azar was identical with what had always been known as "malarial cachexia" for centuries in Lower Bengal—but which we now know to be not malarial but for the most part the sporadic form of kala-azar—so I was compelled to conclude: "The disease, then, is a very intense form of malarial fever," adding: "It is, however, open for any one to say that there is something in the disease in addition to malaria which I have not discovered but which accounts for the spread of the infection." The mode of spread of the disease was also carefully studied, and I was enabled to make some practical suggestions, the success of which has exceeded my most sanguine expectations, as will be seen later. My view was largely accepted in Assam, although some still thought it was a new disease; but the main difficulty in regarding malaria as an infectious disease largely vanished when Ronald Ross's classical researches on the communication of malaria through the mosquito were published, and still more when this great authority on malaria, after a personal investigation of kala-azar in 1899, endorsed my opinion, and concluded after a careful discussion: "I think then, with Rogers that kala-azar is malarial fever."

To return to the progress of the epidemic, we now arrive at a critical point, for the disease had reached the beginning of a narrow tract with but few inhabitants between the low Mikir Hills and the Brahmaputra River, which stretches for some 40 miles before opening out

again into the broader plain of the Golaghat subdivision of the Sibsagar district. I travelled through this country, and found it to be still free from the dreaded kala-azar; but people from the affected tracts of Nowgong were already beginning to move towards Golaghat, and if nothing was done it could only be a matter of time before the open, more populated Upper Assam Valley became infected, and the most favourable opportunity which had yet occurred of staying the epidemic would be lost for ever. I, therefore, strongly urged in my report that infected persons should be prevented from traversing this area, and gave directions for dealing with any villages which might be attacked, and these measures were promptly sanctioned and put into operation by Sir Henry Cotton.

The subsequent history shows a steady decline in the prevalence of the disease, with the exception of slow extension in the already-infected Darrang district north of the Brahmaputra River, although, owing to the population being much scattered in this, as in all the northern districts of the Assam Valley, its ravages have been less here than in Nowgong and other earlier infected parts. In 1898 the fever death-rate began to decrease in the Nowgong district, while an inquiry showed that it had not yet advanced into Sibsagar, and "precautions had been taken to treat all suspicious cases on the frontier, and check the further advance at the outset." These measures have proved eminently successful. for, although a small outbreak did actually occur in 1899 on the borders of Golaghat, the cases were promptly isolated, and the epidemic never gained a firm foothold in this district, and no increased fever mortality has appeared there, while the marked decline of the epidemic in Nowgong during the next three years has now largely removed the danger of its further spread eastward. In 1901 the epidemic is said to have almost died out of the Goalpara and Kamrup, while parts of Nowgong were quite free, and only chronic cases were to be seen in the rest of the district. In the following year very little of the disease remained even in Nowgong, although it still continued in scattered villages in Darrang, but showed little of its original powers of extension.

In 1902 the medical profession in India were startled by yet another theory concerning the nature of the disease, for Dr. Bentley of the Darrang district announced that kala-azar was nothing but an "epidemic Malta fever," on the strength of serum reactions in 75 per cent. of a small series of cases, in dilutions of only 1 in 10 to 1 in 40, obtained at the Kasauli Institute, although in a previous series he had sent to me as cases resembling Malta fever I had not been able to obtain any positive reactions. Further observations which I made with the Malta fever organism, kindly supplied me by D. Semple, R.A.M.C., of Kasauli, showed that reactions in the low dilutions mentioned could occasionally be obtained with the blood of other diseases than Malta

fever, and it has been since acknowledged officially that such low dilutions as had been employed in the kala-azar tests were of no diagnostic value, while Dr. Bentley has now recanted his theory.

In 1897, the year of the great earthquake, the fever death-rate in Sylhet, to the south of the Khasia Hills, rose to 30.89 per mille, or over double the normal rate, and was 19.14 the following year, declining again to 15.38 in 1900, and falling steadily during the succeeding lustrum to only 8.73 in 1905, showing clearly that the increase was a temporary one due to the marked physical changes produced by the earthquake, and not a prolonged wave such as was always caused by epidemic kala-azar. Nevertheless, the temporary increased fever mortality naturally led to careful inquiries, and in 1900 kala-azar was reported to be widely prevalent in the Sylhet district, while in 1904 the civil surgeon stated that "kala-azar occurs, though not epidemically, throughout the valley, and that malaria is very prevalent"; and he also found in some of the cases the protozoal parasite of the disease, which had by this time been discovered by Leishman and Donovan. A careful study of these reports and of the district death-rates has convinced me that kala-azar is only present in the Sylhet district in the sporadic form, just as it is in the neighbouring districts of Eastern Bengal, and as I had found it to be in 1897, when I visited Sylhet for the purpose of seeing "malarial cachexia" in a district free from the epidemic kala-azar. Indeed, it was the very close resemblance between the sporadic cases always known as "malarial cachexia" in Sylhet and Lower Bengal, with those of the Assam epidemic, which forced me to the conclusion that the more serious spreading affection was but an intensified form of the sporadic "malarial cachexia"; and this view is now seen to be correct, with the all-important modification introduced by the epoch-making discovery of the parasite of kala-azar—namely, that the great majority of the cases hitherto known as malarial cachexia in Lower Bengal, as well as in Madras, are not malarial at all, but due to the recently-discovered parasite of kala-azar.

This occurrence of the sporadic form of the disease in the Sylhet district, as well as in Mymensingh in Eastern Bengal, also serves to explain why the epidemic form did not spread into those districts, but passed round the north side of the Garo Hills into the virgin soil of the Brahmaputra Valley, previously free from the sporadic disease, and, finding there a population fully susceptible to its deadly influences, it worked the most terrible havoc. It thus becomes clear that unceasing vigilance must continue to be exercised against the insidious extension of the disease into the still unaffected eastern portion of Brahmaputra Valley as long as the disease lingers in Darrang, while a careful watch must be kept to enable prompt measures to be adopted should further unhealthy seasons originate a fresh outbreak in the same way that the epidemic was started at the foot of the Garo Hills in 1875.

The Effect of the Epidemic on the Fever Death-rate and on the Population.

I have now traced the course of the epidemic, but in order to give some more definite idea of the disastrous effects of the fever wave, which has spread through some 300 miles of the Assam Valley during the last thirty years, I have prepared a diagram (Diagram II) showing in elevation the annual number of deaths returned as due to fever in each of the districts traversed. The death-rates per mille of population are also shown in the dark lines, but present some irregularities due to their being calculated on fresh census figures in 1890 and 1900. As the death-rates for the Garo Hills are not available, the first district to be dealt with is Goalpara, the smaller southern part of which alone was severely affected by the disease. Only the figures for the whole district are available ; but, nevertheless, they show a marked increase of the fever death-rate from 1883 to 1888, followed by a steady decline, only broken by increases due to influenza in 1891, and to famine and earthquake respectively in 1896 and 1897.

Coming next to the Kamrup district, we find again a marked fever mortality wave a little later than that in Goalpara, namely, from 1888 to 1894, followed once more by a steady fall, except for the later unhealthy years already mentioned, to reach much the same rate as before the outbreak, clearly showing how definite is the decline of the epidemic disease, although it doubtless leaves behind it some sporadic cases of kala azar.

It is not, however, until we come to the Nowgong district, the whole of which was swept through by this deadly fever, that the full magnitude of the disaster to such a thinly-populated country as Assam is clearly seen. Beginning to suffer in 1892, when Kamrup was past its worst, the fever death-rate rose by leaps and bounds from an average of about 4,000 a year previously to 1892 up to over 14,000 in 1897, and then declining still more rapidly to under 6,000 in 1900, and an average of about 4,000 once more during the last five years. The completeness of this fall, however, is partly due to the frightful depopulation of the district by the epidemic, for the death-rate per mille during the last few years averaged about 15.5 against 13 before the outbreak. The broken line indicates the birth-rate per mille of Nowgong, which also shows a marked decline during the height of the epidemic, as might have been expected, and helps to explain the great decrease of population to be referred to presently.

Next we come to Darrang, which shows a less accentuated and more prolonged wave of increased fever mortality, due to the slow spread of the disease through this extensive district. Much of the increased number of fever deaths here shown, however, is due to the rising population from extensive immigration; and on turning to the fever deaths per mille we find that the kala-azar wave extended from 1894 to 1899—that of 1892 having been due

to influenza—during which the rate rose from 20 to 30 per mille, falling again to an average of 23 during the last six years, a rate which is still above the average of 18 per mille before the invasion of kala-azar, thus indicating a lingering of the disease in the last affected eastern portion of the district, which still to some extent threatens the Sibsagar and Lakhimpur divisions.

In the lowest part of the diagram the fever rates of Sibsagar are given, the increase of the total numbers returned being solely due to increase of population; for the death-rate per mille is much the same as it was thirty years ago, thus demonstrating that there has been no in-wave of increased fever mortality in this area, such as occurred in the kala-azar infected tracts, and proving beyond doubt the success of the measures I advocated for preventing the devastation of this and the Lakhimpur districts, which contain a most important part of the Assam tea industry.

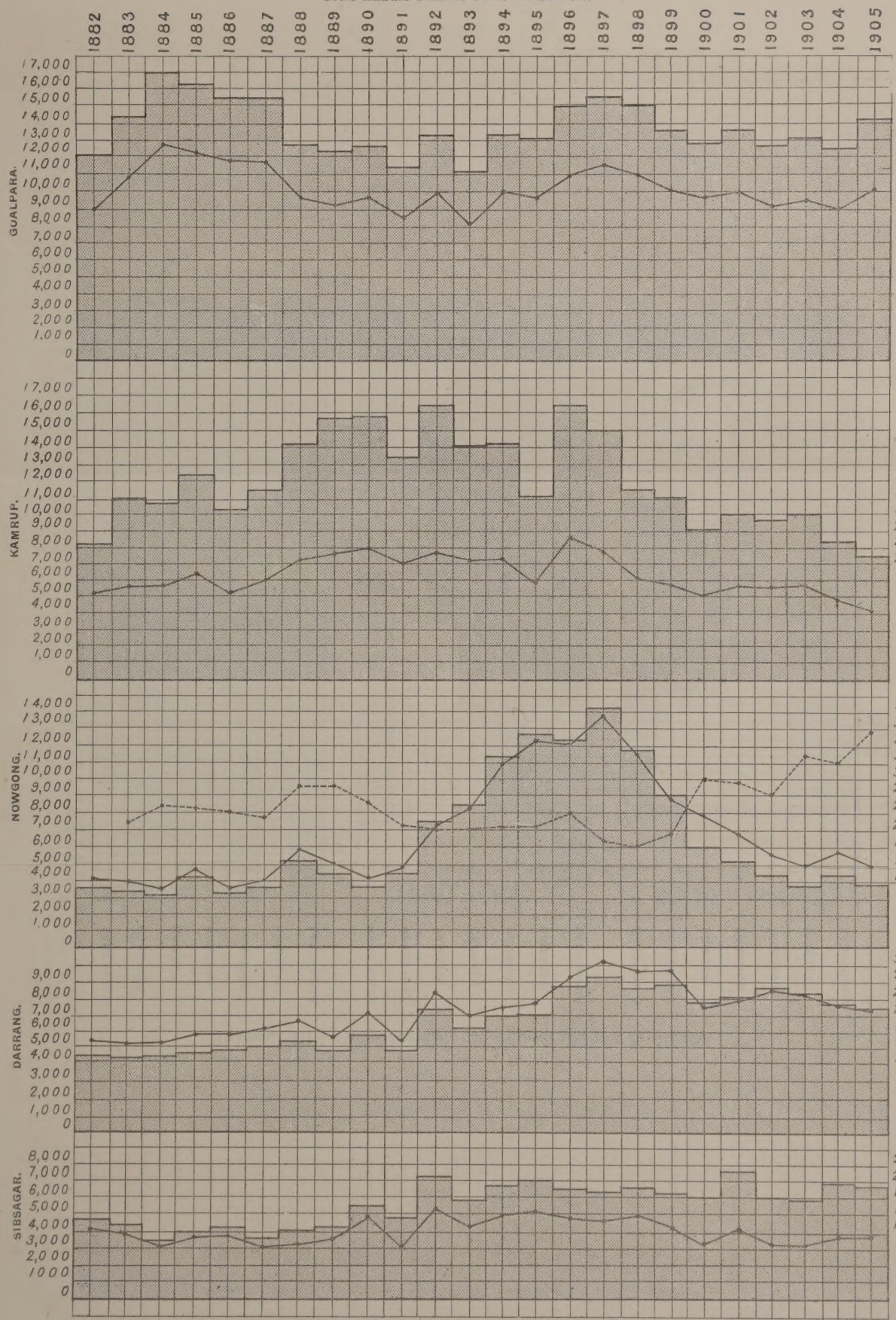
Diagram III, showing the effect of the disease on the population of each district, as revealed by the figures of the last four censuses, speaks still more eloquently as to the terrible nature of the disaster. The variation in the indigenous population of each district, after allowing for immigration and emigration during the last three decades is shown in the order in which they were attacked from left to right. The first part shows but a slight increase in the Garo Hills between 1872 and 1881, during part of which period the epidemic was present there. On the other hand, the remaining districts revealed a marked increase in the population varying from 10 to 24 per cent.

The second part of the diagram illustrates the variations in the population of the same districts between 1881 and 1891, during which kala-azar overran the southern parts of the Goalpara and Kamrup districts, and began to invade the western Mangaldai division of Darrang. The unshaded portion below the line marked 100 shows the decrease in the population of the Goalpara subdivision in this decade to have amounted to no less than 18.08 per cent., against an increase during the same time in the northern unaffected part of the district of 19.36 per cent., which Mr. A. E. Gait, the Census Commissioner, estimated to mean that the "ravages of kala azar are chiefly responsible for a reduction of 29,699 persons" in this subdivision. Again, there was a decrease of 1.6 per cent. in the population of Kamrup in the same decade, against an increase of 14.9 per cent. in the previous nine years, which Mr. Gait calculated meant a loss of 75,000 persons from the disease. Here, again, the decrease on the south, or badly affected, part of the district was 12 per cent., against an increase of only 2 per cent. on the north bank of the river. Darrang shows a stationary population in this period due to the invasion of Mangaldai, against an increase of 10 per cent. in the previous one.

The third part of the diagram shows similar figures, for from 1891 to 1901, during which the population of the

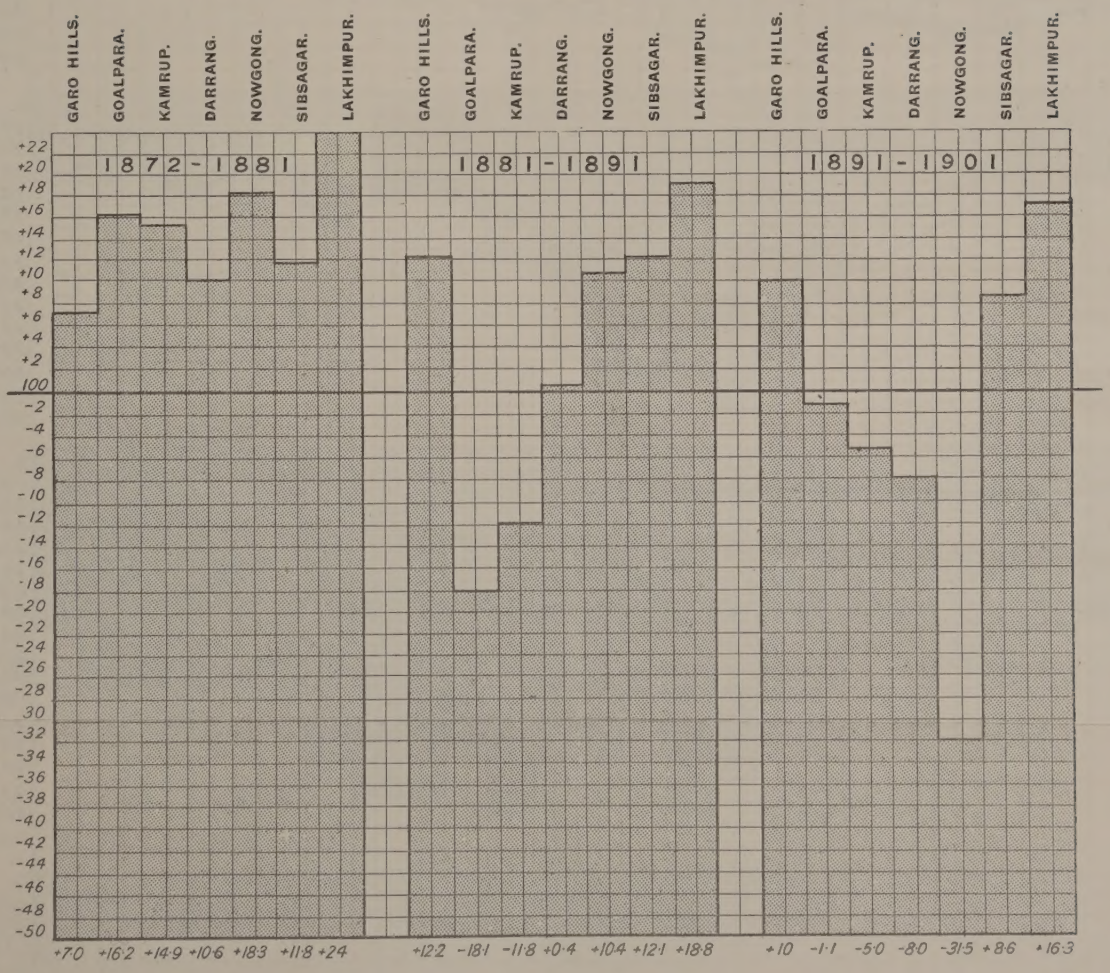
DIAGRAM II —*Assam District Fever Death-rates 1882-1905.*

Total Annual District Fever Death-rates.



Fever death-rates per mille shown by dark lines. Birth-rate of Nowgong shown by broken line.

DIAGRAM III.—*Census Increase or Decrease of District Populations.*



Goalpara district was practically stationary, Kamrup showed a loss of 5 per cent., and Darrang of 8 per cent. of its people. During this decade Nowgong felt the full force of the epidemic, and its truly appalling nature is revealed by the fact that in these ten years, instead of an increase of 10 per cent., as between 1881 and 1891, there was actually a decrease of 24 per cent. of the total population of the district; or, if the indigenous Assamese are alone considered, the loss was no less than 31.5 per cent., or almost one-third of the people—a death-rate which far exceeds that of recent plague, and for which it would be difficult to find a modern parallel, unless it be that of the closely-allied sleeping sickness of Africa. On the other hand, Sibsagar and Lakimpur again showed a substantial increase of the population, after allowing for immigration, indicating once more that this part of the valley was still unaffected by the disastrous fever. Moreover, the land has fallen out of cultivation in proportion to the loss of the inhabitants, for some figures kindly supplied to me by Mr. Gait showed that one-fourth of the land in the affected parts of Mangaldai was abandoned within five years, and one-fifth of that of Nowgong within a similar period ending in 1895, before the outbreak had nearly exhausted itself; while no fewer than 54,179 persons were estimated to have died of kala-azar alone in this district in nine years. I myself frequently saw patches of grass jungle springing up in the midst of rice fields, and on inquiry always found that it had belonged to some family which had been exterminated by kala-azar shortly before, no one being left to till the land, which also lost its value completely as there was no demand for it. Happily this particular outbreak appears to be practically at an end, but it behoves us to study it carefully so as to be prepared to check at its outset any future epidemics which may arise, and also to inquire into any previous outbreaks of a similar nature, from which further lessons of a practical nature can be learnt.

The Burdwan Fever Epidemic of Lower Bengal, 1856-73.

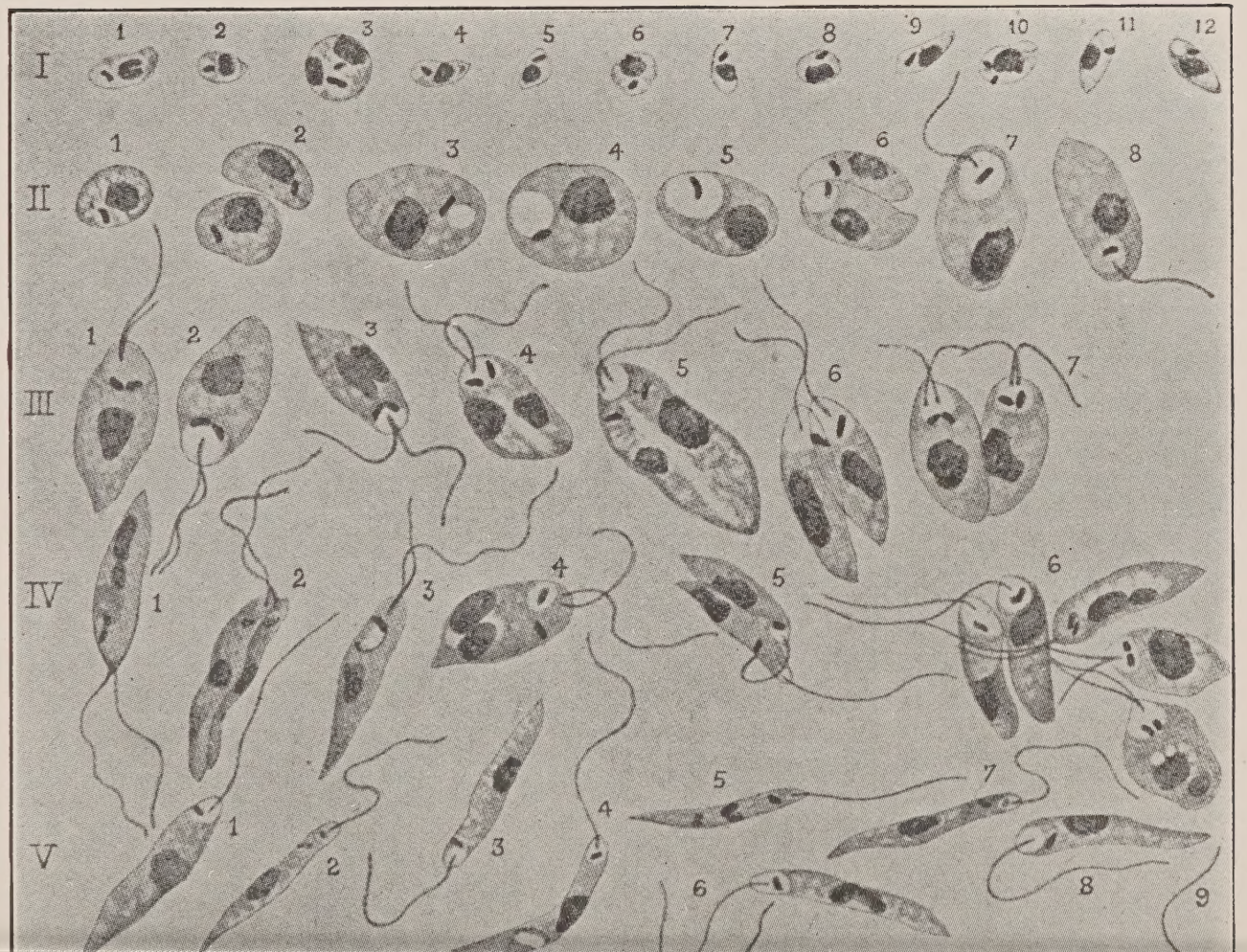
When studying the literature of kala-azar I was struck by the similarity of its main features to those of a previous fever outbreak in Lower Bengal, known as Burdwan fever, from the name of the district it chiefly affected, and a close examination of the records of the latter disease convinced me that the two epidemics were of the same nature, although independent of each other, so that the kala-azar of Assam is not an isolated phenomenon. I have dealt with this Bengal fever elsewhere, so need only now recall its main features. It began in Jessore, to the east of Calcutta, where it reached its height in 1854-5, and then began to spread through Nadia from 1857 to 1864, while in 1862-3 it invaded Burdwan division, in which its course was carefully traced in a very excellent report by

Dr. Jackson, the Sanitary Commissioner of Bengal, in 1872. He pointed out that it spread along roads and lines of communication, and was checked by the absence of ready intercourse between different villages. Further, ultimately stopped when it reached the edge of the alluvial soil, as it failed to gain a firm footing on the drier laterite, and in the hill tracts of Chotta Nagpur, just as kala-azar was limited by the higher hills surrounding the Brahmaputra valley. Owing to the density of the population of the affected parts it is said to have carried off no less than one quarter of a million people in the Burdwan division alone, and it converted this previously very healthy district into a still notoriously feverish part. The exact nature of the disease gave rise to almost as much controversy as its Assam prototype, the question of its contagiousness especially being warmly debated. Dr. Jackson concluded: "While I believe the fever to be malarious in its origin, and to have some malarious characteristics, I believe it to be not a simple, but a contagious, malarious fever; that is, probably typho-malarial, and that it was not produced in Burdwan but imported." I have recently found the parasites of kala-azar in some sporadic cases of the disease from Burdwan, so this outbreak seems to have permanently left behind it the endemic form of the disease.

Kala-dukh.

Another smaller outbreak of a similar nature, described under the name of kala-dukh by E. B. Brown, I.M.S., in 1898, occurred in the north-east corner of the Purneah district, immediately adjoining Dinajpur, and hence doubtless an offshoot of the great Rungpore-Dinajpur fever outbreak which gave rise to kala-azar in Assam. Kala-dukh depopulated a number of villages in the Nepaul terai; but when I visited the place in 1904 it had nearly completely died out, only a few chronic cases remaining, while in the neighbouring part of the Dinajpur district there were fairly numerous sporadic cases of the disease, in some of which I found the parasites of kala-azar, thus establishing the identity of this small outbreak with the more extensive ones already described.

I have now completed my survey of the subject from the epidemiological point of view, having treated it in considerable detail, because I think the vast economic importance of these terrible spreading fevers is not yet fully realized out of India, and that the necessity of clearly distinguishing between the epidemic and the sporadic forms of the disease cannot be too strongly insisted on. The two disastrous outbreaks I have described both occurred within the last half century, their spread being conceivably assisted by improved communications in the affected tracts; and, as it is impossible to say when a fresh epidemic may be started, we must be on our guard against them, for in no disease is it so true that knowledge is power, as I shall hope to show you in the course of my remaining lectures.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LECTURE II.

KALA-AZAR AS A DISEASE.

In my first lecture I dealt with kala-azar as an epidemic, tracing its origin, spread, and decline, and referred to a similar earlier outbreak in Bengal known as Burdwan fever. To-day I pass on to describe the disease itself—its course, complications, and terminations—and shall show you that it is not one whit less terrible when considered individually than collectively, for it literally kills by inches after most prolonged sufferings, which we are still powerless to check to any great extent. As the later stages of the disease are much better known than the earlier ones, it will be clearer if I first describe the typical advanced condition, returning to the still rarely recognized commencement of the fever.

The General Appearances in the Characteristic Stages of the Disease Kala-azar.

A number of lantern slides showing groups of cases were shown, and the salient points of each pointed out, the main features being the marked contrast between the tumid bellies due to the very great enlargement of the spleen, and sometimes also of the liver, contrasting with the great wasting of the chest, face, and limbs. Brief notes were given of a group of hospital cases which illustrated the different courses the disease might take, while a village group showed the great frequency of the affection in children, just as in malarial fever, the incidence decreasing steadily in the subsequent decades. Other groups of sporadic cases, then known as "malarial cachexia" in the Sylhet Valley, which was not invaded by the epidemic, showed the clinical identity of the two forms of the disease, which was the principal argument of the speaker in his 1897 report in favour of his view that the epidemic disease in the Brahmaputra Valley was but an intensified form of malarial fever. The extreme wasting in the last stages and the dropsical ascitic form produced by a peculiar form of intracellular cirrhosis of the liver were also illustrated.

Family Distribution.

Several of the cases already referred to illustrate very well the extraordinary tendency of this disease to attack a number of persons in the same family or household, but the frequency with which this is the case will be better realized from the following figures relating to twenty successive Assamese patients seen in the Nowgong Hospital. Among their near relatives no less than 123 persons had been attacked by kala-azar, only 2 of whom recovered from it, while but 44 of their near relatives had escaped the infection; or to put it another way, no less than four-fifths of these patients had lost half or more than half of their relatives within three to five years, so that it is easy to understand how whole families have been destroyed, and so much land has fallen out of cultivation.

A similar family incidence is seen in the sporadic disease, and is best illustrated by European series of cases, in whom it is easier to follow up the histories. An examination of my notes of the Calcutta European Hospital cases of the last six years shows that the most common relationships between patients actually in hospital for the disease were parent and child in six instances, and brothers and sisters in seven more, nearly always children, while in no less than three of these instances more than two children of the same household were admitted, the series in one family extending over a period of five years. Moreover, just one-third of the whole series of cases had relations actually in hospital during this period, while a good many more gave histories of other members of their families being attacked with fevers of long duration, which were pretty certainly mostly of the same nature. This family incidence clearly points to a house infection, and was the basis of the successful measures I advocated against the disease.

The histories of the rare cases in which Europeans in Assam were attacked by kala-azar throw some further light on this question, for in all the 6 cases, regarding whom Dr. Dodds Price kindly furnished me with information, the affected men were in the habit of cohabiting with native women either in the infected lines or in three instances with one woman, who was subsequently found to be infected with kala-azar, two of them eventually dying of the disease. Two of these last cases of infection were most important, as they occurred in parts then uninfected with kala-azar, but in each case the woman had come from an infected district. Moreover, Dr. Price knows of no instance in which a European cohabited with an infected native woman who escaped kala-azar; and when we bear in mind that it is the usual custom for such women only to come to the bungalow at night and not to eat with the European, then it becomes clear that the most likely mode of infection by a parasite occurring in the peripheral circulation is through some biting insect, in which the parasite may pass its extracorporeal stage of existence. Moreover, such a source of infection may furnish a clue to that of adult Europeans, with no family

history to explain it, in large towns such as Calcutta, as well as among soldiers in Bengal cantonments, and is also in accordance with the decreasing age incidence after early adult life. Again, the infection of one child after another in the same house may be also readily explained on the same hypothesis, and indicates the importance of isolating—at least, in a separate room—any person attacked by the disease, or, better, in a hospital where persistent treatment and nursing can be carried out.

Age and Sex Incidence.

Among tea-garden coolies, who furnish the most accurate statistics, there was no difference in the incidence of the disease on the two sexes, nor did occupation affect it. Numberless instances of husband and wife being infected one after the other were met with, it being, in fact, the exception for one of them to escape—another striking instance of house infection. In the sporadic disease in Calcutta an excess of native males are admitted, much in proportion to those of other diseases. In the European hospital there were twice as many males as females above the age of 15, possibly partly due to the source of infection just mentioned; but in children under 15 there were 23 females to 13 males, probably due to a larger proportion of the male children living away from home at schools.

The age incidence is of great importance, the most striking fact being the number of children attacked. In my report I recorded that 25.6 per cent. of my cases occurred in children under 10, while 24.4 per cent. more were between 10 and 20 years old, making 50 per cent. under the latter age. Further, in a more recent report on the sporadic disease in Sylhet, 39 per cent. were under 10, and 30 per cent. more between 10 and 20, making nearly 70 per cent. under 20. Among natives in Calcutta only 8 per cent. were in children under 10, but 40 per cent. between 10 and 20, three-fifths of which were boys from 10 to 15, who are much more readily brought to hospital than girls or younger children. Between the ages of 20 and 30 were 32 per cent., 16 per cent. from 30 to 40, and only 4 per cent. over 40 years of age. Among Europeans, who readily bring their children to hospital, 20 per cent. were under 10, and 22 per cent. more between 10 and 15, making no less than 42 per cent. 15 or under; 22 per cent. from 20 to 30, and 20 per cent. over 30, showing once more a very high rate among the unfortunate children, and a decreasing one with advancing years.

Race Incidence.

It has already been mentioned that epidemic kala-azar was rare in Europeans in Assam compared with natives, but is not so very uncommon in Europeans in Calcutta in the sporadic form. The class of Europeans attacked is here of great importance, for out of 87 cases, regarding whom I have a note as to how long they had been in India, I find that no less than 87.34 per cent. were born

and bred in that country, and only 12.66 were immigrants from Europe. Moreover, the shortest time after arriving in India that any immigrant was attacked was eight years; a second had been thirteen years, and a third nineteen years in the country; while the remaining eight had all been over twenty years in India, and belonged to the same class as those born in Calcutta, and, like them, were living in parts of the city where their houses were surrounded by those of native inhabitants and under conditions of overcrowding and bad sanitation. In fact, almost all these unfortunate people belonged to the poorest sections of the mixed European and native population, among whom the sanitation and cleanliness of the well-to-do official and commercial European immigrant class is an impossibility—a fact of great importance in connexion with the etiology of the disease. In marked contrast with this is an observation I have recently made to the effect that 80 per cent. of the European immigrants admitted to hospital for typhoid in Calcutta had been three years or less in India, for the totally different incidence of sporadic kala-azar just mentioned in this class will prove a useful point in the differentiation of the later disease in its early remittent stage from typhoid, with which it has been so much confused.

Seasonal Incidence.

Owing to the disease lasting from a few months to several years, cases are admitted to hospital at all seasons, and neither in Calcutta or Madras is there any very marked seasonal incidence, although there is some excess of admissions of Europeans in Calcutta at the end of the cold and beginning of the hot season, especially among those coming in the early stages of the fever.

Of much greater importance is the question whether the fever begins at any special season, as is suggested by the fact that the extra-corporeal stage of the parasite, to be described later, only developed in my cultures below a temperature of 75° F. It is very difficult to obtain accurate histories of the beginning of the disease in many cases, especially when they are seen for the first time at a much later date, but an analysis of my notes of those who stated they had had fever for not more than six months in two series of cases (in the Native Medical College and European hospitals respectively), both showed a marked preponderance commencing during the cold weather, or early in the hot weather, on account of the frequent long incubation period. These results can be summed up by saying that in the six months from November to April there were three times as many cases in the European series and almost four times as many in the native one as in the remaining six months of the year—a sufficiently striking fact when the difficulties of getting accurate data are considered. When in Assam I tried to work out this point from the admission to hospital for fever on tea estates, and found that most of the patients suffering from

typical kala-azar in the cold season had been admitted for short attacks of apparently malarial fever in the previous rainy season from June to October, but few escape malaria at that time. On finding the sporadic cases in Calcutta mostly began in the cold season in Calcutta, I wrote to Dr. Dodds Price for his matured experience on the subject, and he very kindly sent me histories of all his European cases, every one of which had commenced in the cold weather; while an inquiry into his, then comparatively few, native patients also showed that almost all of them had developed kala-azar during the cold weather, and he added, "All this is very instructive, and fits in exactly with your Calcutta experience."

Taking everything into consideration, I think there is sufficient evidence to prove that the great majority of patients become infected in the cold season, and I am inclined to think that infection will ultimately be found to be limited to this time of the year. The importance of this fact in connexion with prophylactic measures is clear, as it will greatly simplify matters if precautions against infection have only to be taken during a few months of the year.

The Types of Fever.

I now come to the difficult subject of the diagnostic value of the types of fever in kala-azar, my conclusions being based on four-hour temperature charts of every case in the European Calcutta hospital for several years, and a still larger series in native patients; while as I also possess complete notes and charts of every fever case in the open wards of the European hospital for two years I am now in a position to point out the most important features in the diagnosis of kala-azar in the difficult early stages from other fevers with which they are commonly confused. The lantern slides prepared from the charts, some of which represent the temperature curves for several months, will best serve to illustrate the types met with.

The principal points illustrated by the charts shown were the following: The very long duration of the fever, which shows alternating remittent and intermittent types for many months at a time, even in the case of patients admittedly in a markedly cachectic and anaemic condition, showing the great resisting powers of the patients. When the temperature is of the remittent type there is rapid wasting and impoverishment of the blood, but when it falls to the low intermittent type, both the weight and the blood show steady improvement, while quinine in large doses has a marked effect in reducing the high dangerous type of fever to the low, comparatively harmless one, which may eventually wear itself out and cease entirely, when the weight is soon regained; and once the patient has been free from fever for several months, and fully regained the normal weight, relapses are rare and recovery is permanent and complete. Such cessation of the fever and cure sometimes follows a severe septic complication,

such as cancrum oris, and is then accompanied by a marked rise in the previously very low number of polynuclear leucocytes, which the writer has also been able to produce, with good results in a few cases, by injections of sterilized cultures of staphylococci in accordance with the methods of Sir Almroth Wright, although it has not been invariably successful. The good effect of large doses of quinine was illustrated by a nine months chart of a child of 8, seen early in the disease, and whose fever was only finally broken when 50 gr. of quinine had been taken daily for seven weeks; her weight also steadily rising from the time this large dose was given, and no ill-effect being produced by it.

The recognition of this fever in its early stage, which usually begins with a high remittent form of pyrexia, may often be accomplished by noting the certain peculiarities in four-hour temperature charts. The most important of these, which is illustrated by the slides shown, is what I have already described as the double remittent type, namely, a marked daily double or even a triple rise of the temperature, often for several days together, in the absence of any treatment by the more powerful sweat-producing antipyretic drugs such as antipyrin. This double type is most frequently seen in the earlier periods of the fever, but may occur at any time in its course, and may also occasionally appear during continued or intermittent pyrexia in kala-azar. The great importance of this type is that, in my experience, it is never seen in typhoid fever, for which the early stage of sporadic kala-azar is so frequently mistaken, as in some of the cases illustrated, and this type is almost diagnostic of the new fever, the first case in a European in Bombay having been first suspected on account of the double remissions taking place. Another type of fever shown in the charts, which is rather characteristic of this fever, is a low continued type of pyrexia, the temperature falling below 101° F., but not varying more than two degrees in the twenty-four hours; a type which is much rarer in typhoid, in which the pulse is also usually slower than in kala-azar in proportion to the degree of the pyrexia. Moreover, even when the fever is high for long periods in kala-azar there is a characteristic absence of severe distress or typhoid symptoms, patients often saying they feel quite well, and do not think they have any fever, when the thermometer registers 103° F. or 104° F. Once more, when the remittent temperature falls it commonly assumes a low intermittent type, rising to about 100° F. every afternoon, instead of running a subnormal course, as after typhoid, a feature that will often allow of the more serious kala-azar being suspected at an early date before the cachectic stage has been reached. A consideration of these various types will nearly always allow of the sporadic affection being suspected at an early date, when persistent treatment is most likely to be of avail, while the blood changes will allow of the diagnosis being confirmed.

The Spleen and Liver in Kala-azar.

Time will not allow of my giving a full clinical account of this remarkable disease (although I hope to do so shortly in a work on Fevers in India, for which I have been collecting material for a number of years), but a few of the more salient points must be touched on.

The Spleen.—The great degree of enlargement of the spleen can best be indicated by the following data. In 70 typical advanced cases of the epidemic disease in Assam of which I have notes, the spleen was enlarged in all, while in 94.5 per cent. it reached to at least 3 in. below the costal margin, in 56.5 per cent. it extended to the navel or beyond, and in 27.7 per cent. to the level of the anterior superior spine of the ilium. In 95 consecutive sporadic cases in the Medical College, Calcutta, all verified by finding the parasite in the spleen blood, in 80 per cent. the organ reached to the navel or beyond, and in 10 per cent. to the anterior superior spine of the ilium. In a series of earlier sporadic cases at the European general hospital the spleen extended to the navel or beyond in 63 per cent., being nearly always of this size in cases of over three months' duration, although the edge was above the navel in three fifths of the cases with under one month's history of fever.

On the other hand, among 200 healthy coolies I examined in Assam on a tea-garden when unaffected with kala-azar, I found only 1 per cent. with spleens reaching down to the navel, in only 6 per cent. did it extend 3 in. below the ribs, while in a total of 25 per cent. the organ could be felt below the ribs—figures which suffice to disprove Dr. Giles's statement that it would be absurd to attach any importance to enlargement of the spleen in kala azar in such a malarious country as Assam.

The liver was enlarged in 43 per cent. of my Assam series, in 75 per cent. of the Medical College, and in 59 per cent. of the European cases in Calcutta who came earlier under observation, it having been normal in seven-eights of the European patients admitted during the first month of the fever. The enlargement of the liver to any marked degree is very uncommon in the earlier stages, although after some months it may occasionally reach down to the navel, and may then be even larger than the spleen, and eventually become cirrhosed, causing ascites.

The Blood Changes.

I have elsewhere described the blood changes in kala-azar, and pointed out their great value in differentiating it from other diseases, especially fevers, so need only now summarize them. In the first place, an increase in the percentage of the large mononuclear leucocytes is very common, and of great value as a point in the differentiation of the early stages of sporadic kala-azar from typhoid fever, for in the latter the lymphocytes, but very rarely the large mononuclears, are increased during the pyrexia. On the other hand, this change is of no help in dis-

tinguishing kala-azar from true chronic malaria, in which a large mononuclear increase is also commonly present. These two last diseases may, however, be distinguished by counting the total red and white corpuscles and working out the proportion between the two; for in malaria both are about equally reduced, so that the ratio of white to red remains normal, namely, about 1 to 750, and very rarely, if ever, falls below 1 to 1,000, while in kala-azar it is the rule for the white corpuscles to be disproportionately reduced, so that the ratio of white to red is—in the absence of any leucocyte-increasing complication — commonly below 1 to 1,500, and not rarely as low as 1 to 2,000, 3 000, or more. This extraordinary reduction of the leucocytes, which not rarely number but from 500 to 1,000 per c.cm., is almost diagnostic of kala-azar, as I have never met it in any other fever cases out of some hundreds in which I have done blood counts, and it has often enabled me to diagnose the disease in a comparatively early stage. So much is this the case that I now rarely employ the spleen puncture as a diagnostic measure, several fatal cases, in addition to those published, having come to my knowledge. It should never be done in very anaemic patients, or in those who have suffered from any form of haemorrhage, unless the blood is first proved to be clotting normally, while I always take the further precaution of keeping up digital pressure for several minutes after withdrawing the needle, and immediately administering a dose of calcium chloride by the mouth. With these precautions it may be of value in some difficult comparatively early cases in which the confirmation of the diagnosis is of great importance, in order to allow of continued and adequate treatment being strongly urged on the patient, so many of whom leave hospital during a temporary remission of their fever, and leave off the all-important quinine until a fresh high remittent bout comes to reduce them another step towards the grave.

Complications.

The frequency with which kala-azar is terminated by some inflammatory complication has already been mentioned and may best be illustrated by the data from 40 necropsies made by me at the Medical College Hospital. All but 7 of them showed some serious local disease, and some of them more than one. In 11 pneumonia, in 10 dysentery, in 7 cancrum oris, in 2 each pneumococcus meningitis, purpura, cerebral haemorrhage, and phthisis respectively, and in 1 pericarditis were found, while in several cancrum oris cases staphylococci or streptococci were cultivated from the spleen, revealing a general septic infection. The extreme reduction in the polynuclear leucocytes in this disease, in which they not rarely fall to one-twentieth or less of the normal numbers, easily explains the frequency with which these patients fall victims to the specific organisms of pneumonia, dysentery, phthisis, or the cocci of cancrum oris, in which I have

never been able to find the diphtheria bacillus, which has been met with in European cases of this disease.

Haemorrhages deserve special mention among the complications, reduced coagulability having been found by me in some of these cases, while bleeding from sloughing ulcers, or from the stomach or bowel, has also been seen, in addition to several cases of bleeding into the brain or its membranes.

Treatment.

Although much has been done to elucidate the pathology of kala-azar during the last four years, unfortunately the treatment of the disease has made no corresponding progress, and is still in a most unsatisfactory state. In Madras, indeed, I am informed that almost every case is believed to die, the mortality being estimated at 98 per cent., the highest figure reached in the Nowgong tea estates by the epidemic form, while that of several hundred cases treated by Dr. Dodds Price at the height of the epidemic gave an average mortality of 96 per cent. Dr. Price's cases were treated with thymol first, to exclude ankylostomiasis, quinine in moderate doses being generally used during the several periods the patients were in hospital, but it was the common opinion that quinine failed to check the fever in the same way it did malaria, and many thought it quite useless and used it very little, as is also the case in Madras at the present time. In my report I strongly dissented from this view, and urged that quinine does have a definite effect in controlling the severity of fever, even when it did not stop it altogether, and recommended that it should be given in large doses, and persisted with for months together if necessary. Several years' further experience in Calcutta has only served to confirm me in that opinion, for I have repeatedly seen a high remittent fever reduced to a comparatively harmless low intermittent one by increasing the quantity of quinine given, 60 gr., and in some cases 90 gr., a day having been taken for considerable periods with nothing but good effects beyond being sometimes distressing to the patients.

Once the temperature has fallen to the low intermittent type, it can often be kept down to that point for a long time, by smaller doses, 20 gr. in the morning being commonly effectual. That this line of treatment gives far better results than those admitted by unbelievers in quinine will be clear from the fact that after the publication of my report, Dr. Dodds Price systematically tried persevering quinine treatment, and when he worked out for me the results of several years' experience, he found that the mortality of 500 consecutive cases was but 75 per cent., the remaining 25 per cent. having permanently recovered, against 4 per cent. in the earlier series quoted above. Now as these patients were indentured coolies, who remained working on the gardens, often for years, after getting over a typical attack of kala-azar (the diagnosis of which in its characteristic stages presents no

difficulties to Dr. Price with his fifteen years' daily experience of the disease, while in some of them the parasite was also found by spleen puncture), there can be absolutely no doubt about their absolute recovery, some of them having also been seen by me both during and after their attacks.

Moreover, these unquestionable results of Dr. Price's are confirmed by my smaller experience in Calcutta under less favourable conditions for following up my patients. Thus, out of 65 cases in the European hospital during the last three years of which I have notes, 18 who left the hospital in a doubtful condition I have not been able to get further news of, leaving 47 other cases. Of these, 21 died either in hospital or after leaving it; 9 more, who left in a worse condition than they came, may be counted as having died—leaving 7, or 14 88 per cent.. who left hospital after having lost their fever and greatly improved, a fair proportion of them probably recovering, and 10, or 21.27 per cent., have completely recovered and are known to have been well for from several months to upwards of a year after leaving hospital. It should be mentioned that three of the patients who recovered had also been treated with injections of staphylococcus vaccine, which appeared to have some good effect.

These figures are in close accordance with those of Dr. Price, and contrast most favourably with nearly invariably fatal results admitted by those who still deny their patients the benefit of persistent cinchonization, although without any efficient remedy of their own, and I venture to think that, in view of the above data, my line of treatment should never be neglected until we have a better one to replace it, as I hope and expect will be the case in time. Bone-marrow tabloids, to repair the blood deterioration, are also of considerable value, while atoxyl, which is now being advocated in the allied protozoal disease, sleeping sickness, is worthy of trial, for my friend, Dr. J. Megaw, I.M.S., has injected it in two cases with at least temporary good effects. Colonel Lukis, I.M.S, Principal of the Medical College, Calcutta, has also tried cinnamate of soda to increase the leucocytes, but without accomplishing the desired result or doing any good; and *x* rays over the spleen have been tried by the same observer, but without effecting any cures. In view of the chronicity of the disease, and the occasional remarkable spontaneous recoveries from an apparently hopeless state, much caution is required in making deductions regarding any line of treatment, but the extraordinary cures which do occur encourages the hope that a better treatment even than the quinine one will be found to rescue these unfortunates from the lingering death which still awaits the great majority of them.

The Distribution of Sporadic Kala-azar in India.

Since it became known that so many cases previously classed as "malarial cachexia" are but the sporadic form

of kala azar, observations on its distribution have been accumulating. Donovan and others have found it to be very common in Madras, while my own observations have shown it to be widely distributed all over Lower Bengal and Assam, except the eastern part of the Brahmaputra Valley. It also occurs somewhat less frequently in Western Bengal or Bihar, and extends into the neighbouring eastern end of the United Provinces of Agra and Oudh, cases in soldiers having been verified by the officers of the Royal Army Medical Corps at Benares, while I have also seen two who appear to have contracted the disease in Allahabad, and others have been met with among Gurkhas as far west as Dehra Dun. On the other hand, during an examination of the records of all the fever cases admitted to the Lahore Medical College Hospital for three years I failed to find any cases resembling sporadic kala-azar, while it is also specially noteworthy that I met with no double remittent, low continued or other doubtful long fevers among them. The Bombay records also show a similar absence of the disease, except rare importations from Madras, so that the disease appears to be limited to the eastern side of India, although I am informed that Burmah, like Bombay, only has cases contracted at Madras.

In connexion with this distribution it is of interest to note that the areas affected all have a very mild cold season, during which the mean temperature for three or four months remains between 60° to 75° F., for I shall show in my concluding lecture that these are the limits between which I have been able to cultivate the parasite outside the human body. On the other hand, in the unaffected north-west parts of India the mean temperature during the cold months falls lower, while owing to the brevity of spring and autumn in India, the temperature conditions most favourable to the organism outside the human body last a very short time in those areas.

Effects of Seasonal Variations on the Prevalence and Origin of the Disease.

I have already shown that the infection of kala-azar is probably limited to the cold season, so an exceptionally long "cold weather" might be expected to temporarily increase the occurrence of the disease. This is actually so, for two years ago such a cold season occurred, and during it and the following early hot weather months an unusually large number of sporadic kala-azar cases were admitted to both the native and European hospitals of Calcutta—many more than in the following year, with a normal cold season. Now this long "cold weather" followed an early cessation of the previous monsoon rains, for the withdrawal of the south-west monsoon is succeeded by a cold north breeze; and it will be remembered that in my first lecture I pointed out that the Assam epidemic arose as a consequence of four out of five successive years of deficient rainfall in the early Seventies, due to an

early cessation of the monsoon current. I have not been able to get complete meteorological data for Rungpore in the Seventies, but those of Calcutta of that period do show that during several of the years of deficient rain the mean temperatures of the ensuing cold season were below the average.

Now, if a single cold year had such a marked influence in increasing the sporadic kala-azar in Calcutta, on account of the longer period which was favourable to the infection, it becomes easy to understand how an unusual succession of such seasons might have increased the number of cases, and so the foci of infection, year by year, until the fever became so widespread that the people began to leave their villages, and thus carried the infection into areas at the foot of the Garo Hills and in the Goalpara subdivision, which had hitherto been almost, or quite, free from it, and so started the spreading disease in Assam in a people who were extremely susceptible to it, owing to not having previously suffered from the sporadic form. Such an origin of the Assam epidemic kala-azar is most in accordance with the known facts, and also with the life-history of the parasite and mode of infection, which I shall deal with in my remaining lecture.

LECTURE III.

THE

LIFE-HISTORY OF THE PARASITE MODE OF INFECTION,

AND

PROPHYLAXIS.

I HAVE now dealt with kala-azar both collectively as an epidemic and individually as a disease, but have still to discuss the evidence I obtained in Assam regarding its infectiousness before describing the life-history of the parasite which produces it.

When I went to Assam in 1896 there was much difference of opinion as to whether kala-azar was infectious or not, the majority holding that as it was certainly malarial it therefore could not be infectious, while a few contended that it was certainly a communicable disease, and therefore it could not be simply malarial in nature, but no one had found time to inquire into the exact way in which it spread. In order to settle this important point I travelled over 150 miles on foot from village to village, and obtained the histories of the introduction of the disease into them from the head men, who return all the deaths, and who were always able to give me detailed information on the subject. Very similar stories were constantly related to the effect that some one suffering from the disease had come to live in the village, usually with relatives, and then others, who resided in the same house, were shortly afterwards attacked, and on the survivors of the first infected household being taken into other families they in turn suffered, while after a year or two the disease became widespread, and frequently from one to two thirds of the people eventually died of it before it began to decrease. Wherever the infection had spread a similar kind of history was obtained, while whenever a village had escaped, although surrounded by infected ones, it was found that for some reason or other they had no communication with each other, even if only a few hundred yards apart. Thus a small village of

Brahmins, who had no intercourse with the infected low caste people around them, escaped, although all the surrounding villages had been attacked for several years. Again, one part of a village, which was separated from the rest by only a few small rice-fields, remained free for years owing to their head man not allowing them to have any intercourse, even with their relations in the infected portion. On the other hand, on visiting a village which was reported to be infected, although all those around it were free, I found that it belonged to people who had recently moved there from a badly-infected part of the district, bringing the disease with them. The extreme steps which the people themselves sometimes took to prevent the spread of the disease is also strong evidence of its infectiousness in their eyes. For example, a girl, who had married a man in a healthy village, but soon after was found to be suffering from kala azar, was turned out, while her own father, in a neighbouring uninfected village, was prevented from taking her into his house, so she was living in a hut erected in the open rice-fields at the time of my visit. The same plan of isolating cases of the disease was adopted by the Garos, who are reported to have gone so far as to render the patients comatose with drink and then burn them in their huts. All the evidence goes to show that the infection is, as a rule, obtained by sleeping in a house with infected persons for a longer or shorter time, in some cases only for a day or two. Moreover, the plan of moving the village to a new site appeared to have a distinctly good effect in lessening the disease when occasionally resorted to by the people themselves, so that I thought the infection might possibly pass through the soil. It was on the knowledge of the infection being largely a house one that I based the prophylactic measures which proved so successful long before the parasite of kala-azar was discovered, but now that we possess much more definite information regarding the true pathology of the disease it will be best to describe the life-history of the protozoal organism of kala-azar before taking up the important practical question of prophylaxis, as the latter will thus be rendered more definite.

The Parasite of Kala-azar and its Distribution in the Human Body.

The parasite of kala-azar was independently found by more than one observer, but to W. B. Leishman, R.A.M.C., belongs the credit of having had the courage to first describe it, two and a half years after he had seen it, as probably a degenerate stage of a human trypanosome, not very long after that organism had been found in a fever in Africa by the late Dr. Dutton, while Rose Bradford and Plimmer had previously described a form of the *Trypanosoma brucei* similar to the bodies Leishman found. As soon as Leishman's paper reached India, C. Donovan, I.M.S., recorded that he had independently observed the same bodies in the spleens of patients dying of prolonged

fever in Madras one month before Leishman's note was published, and as he was also able to find them in fresh spleen blood obtained by puncture of the organ during life, he was able to disprove Leishman's suggestion that they were degenerate trypanosomes, for the flagellate form of the organism has never been found in the human system. Laveran and Mesnil, after examining specimens sent by Donovan, concluded that the organism was a piroplasma, while J. H. Wright of Boston, at the end of 1903, described similar bodies to those of Leishman and Donovan in a form of chronic ulceration met with in the Punjab known as Delhi boil, in which D. D. Cunningham had, as early as 1885, described the aggregations of these peculiar bodies. As kala-azar is unknown in the Punjab there is good reason to believe that the parasite of Delhi boil is quite a distinct species from that of the Assam fever.

In 1896 I had stained smears of kala-azar spleens with aniline dyes without being able to distinguish these bodies, which are not well shown by them, while Romanowsky's stain and its numerous modifications had not then come into common use, and I mainly used fresh unstained blood films, as then advised by Sir Patrick Manson and others, for searching for malarial or other protozoal parasites. The papers just referred to appeared while I was on leave in England, and I quickly realized, as was also suggested by Donovan, Ross, and others, that if many of the cases previously known as "malarial cachexia" were really caused by the new parasites, then kala-azar of Assam must be also produced by it, for I had shown in my report that the Assam outbreak was but an epidemic form of the so-called "malarial cachexia." On returning to India at the end of 1903 I obtained some slides of spleen blood of kala-azar patients from my friend, Dr. Dodds Price, and readily found the new parasites in them, as well as in several cases of chronic spleen fever in the Dinajpur district, which were evidently the sporadic form of the same disease. At about the same time Dr. Bentley independently found the same parasites in kala-azar cases, and published his observations shortly before my own appeared in print. Other cases in Dinajpur with large spleens following chronic fever showed only malarial parasites in their spleen blood; and I found it impossible at a single examination to differentiate between the two forms clinically, although subsequently able to do so by the blood changes, as described in my last lecture. It is not, therefore, surprising that kala-azar has been so long confounded with chronic forms of malarial fever; and the discovery of the new parasite has done more towards clearing up the fevers of Bengal and some other parts of India than anything since Laveran's description of the parasites of malaria. Over a year later, in 1905, S. P. James, I.M.S., also recorded having found the Leishman-Donovan parasites in 67 out of 68 cases of kala-azar, and gave some valuable clinical information regarding the differentiation of this disease from chronic malaria, the discovery of the new parasite

having now furnished the key to the problem which a century of clinical observation has been unable to unlock.

Distribution of the Parasite in the Human Body.

It soon became apparent from the observations of Manson, Low, Ross, and especially of S. R. Christophers, I.M.S. (who had been placed in special duty by the Government of India to work at the subject in Madras), that the organism may be found in practically every organ of the body in variable numbers, although most numerous in the spleen, bone-marrow, and liver. They were also occasionally observed in the mesenteric glands, and more rarely in ulcers in the intestines, and both Manson and Christophers suggested that they might escape in the faeces, and so reach water through which reinfection of others might take place. When a little later I discovered the flagellated form of the parasite, Dr. Bentley announced that he found trypanosomes more commonly in fish from near kala-azar-infected lines than elsewhere, and suggested that they might be a stage of the human parasite. I made some observations in Nowgong to test this hypothesis the same year, but was unable to confirm the correctness of his statement as far as that district was concerned.

Now Christophers's microscopical studies showed that the parasites multiplied mainly in the large endothelial or macrophagic cells of the spleen and bone-marrow especially, until the invaded cells bulge into the lumen of the vessels. During the operation of spleen puncture those containing the largest parasites rupture most readily, and the organisms thus obtained are nearly all the larger capsulated ones in contrast with the many minute ones seen in a spleen smear made *post mortem*. A similar rupture of the distended endothelial cells must also frequently take place naturally in the body, and so allow of the entrance of the parasite into the circulating blood and its distribution to all parts of the body, a hypothesis which also explains the large number of the organisms found in just those organs where the malarial parasites also accumulate—namely, the spleen, bone-marrow, and liver, while I have also several times found them in the brain.

This leads me on to the consideration of the frequency of the parasite in the peripheral blood, for it was the supposed great rarity of such incidence which gave rise to the theory of its escape from the large bowel as the source of infection, which was so generally held before my discovery of the flagellated stage of the parasite. Yet Donovan, Christophers, and James have all met with the parasites within the leucocytes, chiefly in the polynuclears, although no one has confirmed the statements of Donovan, Laveran, and Mesnil, that they may be seen within the red corpuscles, other workers considering that they are only rarely seen lying on the surfaces of the red discs. Recently Donovan has reported that he has found the parasites in the peripheral blood of 75 per cent. of his

cases, while W. S. Patton, I.M.S., now on special duty in Madras, informs me that he detected them in a still larger proportion of specially selected advanced cases. Donovan stated that they are most easily found during high fever, but I have been unable to confirm this, while it is also contrary to Patton's experience, who finds they are commonest in the later stages of the disease, so that it is doubtful if a microscopical examination of the finger blood for the parasites will prove of much diagnostic value in the difficult early stages of the disease. In a few cases I have tried the plan of quickly centrifuging for one minute 2 or 3 c.cm. of vein blood to separate the majority of the red corpuscles, and then making slides of the blood plates and leucocytes after a second longer centrifugation; there was little success, but I think it is worthy of further trial, as it may prove preferable to the sometimes dangerous spleen puncture as a diagnostic method. However this may be, it is now quite clear that the parasites are at least present in the circulating blood in large numbers in most advanced cases, quite sufficiently to readily allow of their entering the stomach of any blood-sucking insect which might form a suitable host for its further development.

The Cultivation and Development of the Flagellated Stage of the Parasite.

Up to July, 1904, the only stage of the parasite known was the small oval body, about the size of a blood plate, with a rounded macronucleus and a smaller rod-shaped micronucleus or centrosome, such as are shown in the first line of the diagram. These multiplied by division, so that in spleen smears a number of very small bodies may be seen in a single cell with no very definite capsule to them, but recognizable by the double nucleus ; or a number of them might be found in a hazy material, first taken for a zoogloea mass, but now known to be but the protoplasm of the cell in which they were growing. It is not surprising, then, that there was much speculation as to the precise class of protozoa to which this organism belonged, suggestions varying from degenerated trypanosomes of Leishman, piroplasma of Donovan and Laveran, spores of a microsporidian of Christophers and an entirely new genus which Ross proposed to call Leishmania-donovani, in honour of the two observers who first described the parasite, being put forward.

As it was clear that we could not expect to gain much further knowledge of the exact nature of the parasite until we learnt something of the extra corporeal stages, and the discovery of such further portions of its life history was alone likely to throw valuable light on the mode of infection of the disease it produces, I set to work on these lines as soon as possible after my return to India, and was fortunate enough to obtain important results. The method employed was to obtain human blood containing the organism by means of spleen puncture and to add

it to about 1 c.cm. of sterile salt solution containing a little citrate of soda to prevent the blood clotting, and to examine it frequently to see what became of the parasites. My first attempts were made at blood heat, with the result that they all died out in a day or two, as other workers had also found. Being struck with the resemblance of the macro- and micro-nucleus of the parasite to those of trypanosomes, just as Leishman had been, and remembering that Laveran and Mesnil had succeeded in keeping the later organism alive for a much longer time at a low temperature than at blood heat, I next tried incubating the citrated blood at about 27° C., and found that in this way they lived for several days, and what is more they appeared to multiply considerably, many dividing forms being present, but as yet without any other material alteration. On next reducing the temperature to about 22° C. (an ice incubator having to be used during most of the year in Calcutta for this purpose), I was soon rewarded by finding that not only did the parasites unquestionably multiply rapidly, but they also increased in size and developed a blue staining protoplasm, and after a time the further development of flagellated forms took place, which were actively motile.

The different stages of this remarkable development are shown in the diagram, which has been made from a plate published in a paper in the *Proceedings* of the Royal Society last year, all the forms in which have been accurately drawn to the same scale with a camera lucida, thus illustrating the extraordinary increase in the size of the parasite as well as in its numbers. Whereas the human stage of the parasite appears to be no larger than a blood plate, and requires careful search with an oil immersion lens for its detection, yet the large rosettes shown in the lower part of the diagram can readily be seen as a stained mass, or in unstained specimens as a lighter circular area, among the red corpuscles with a ½ in. lens. The form in which the parasite is found in the human body is shown in the first line of the plate. The earliest stages of the development, which are shown in the second line of the plate, consist in an enlargement of the macronucleus, without any corresponding change in the micronucleus, which remains a small rod throughout the whole process. At the same time the protoplasm, which is clear in the spleen form of the parasite, now becomes much increased in quantity, and takes on a blue coloration with Romanowsky's stain, Leishman's modification of which was used throughout this inquiry. The next change is a curious one, namely, the appearance in the protoplasm of a rounded mass which takes on the red element of the stain, so may well be termed the eosin body, and the micronucleus is always found to be closely attached to it, while the flagellum arises from it. This form is seen in Nos. 3 to 6 of Line II, while the last two forms of that line show the flagellum arising from it, and apparently separated from the micronucleus by a narrow unstained space, although a study of degenerating

flagellate forms proves that the flagellum is really organically connected with the micro-nucleus, for it comes away from the body with it, as shown in Form X. This flagellated stage rarely appears before the third day in successful cultures, and when the development is carried on under the most favourable conditions (to be described presently), they are found in enormous numbers, and showing all the stages of subdivision, which are illustrated in the third line of the diagram. In this process of multiplication of the flagellated forms the first change is the division of the micro-nucleus and flagellum into two, next the macronucleus also divides, and then a line appears down the centre of the body splitting it into two, the process being quickly commenced again by both the new forms. In this manner the rapidly dividing forms push each other round, as shown in Fig. IX, until they form a complete rosette of No. XII, the flagella all pointing in towards the centre, and in this stage such groups can readily be seen in fresh specimens by low powers with the flagella actively waving in the middle of the mass. Lastly, the individual forms, which up to now are mostly only two or three times as long as they are broad, gradually elongate out and begin to break away as shown in No. XI, to form single exceedingly active organisms, which when stained have the appearance shown in Line V, the eosin-staining micronucleus and flagellum being both situated at the anterior end of the organism, while the macronucleus still remains about the centre. The forms in Line VI are the retrogressive stages of degeneration resulting from contamination of the culture with staphylococci. Forms VII and VIII show early development within a polynuclear leucocyte.

For a long time I was in doubt whether this flagellated form was but a stage in the development of a trypanosome, similar to some of the culture forms of bird trypanosomes obtained by Novy and McNeal on blood-agar medium—a method of culture with which I have failed to obtain success in any stage of the kala-azar parasites. Now that extremely numerous, very active, and apparently fully developed flagellate forms have been obtained, without any tendency for the micronucleus to even approach the macronucleus being seen, much less any sign of an undulating membrane, I have come to the conclusion that the parasite is not a partially developed trypanosome, but another kind of flagellated organism.

Nature of the Parasite.

The discovery of the flagellated stage of the parasite affords much help in classifying it, for now that the life-history of the *Piroplasma canis* has been worked out, and it is known that it has no flagellated stage, the suggestion of Laveran and Mesnil that the kala azar parasite belongs to that genus may be put out of court. It also appears from what has just been said that it is not a trypanosome, and it appeared to me to be more closely allied to the hepatomonas than to any other known flagellate protozoon

As repeatedly sending specimens to English zoologists failed to elicit any opinion on the point, I forwarded some to the late Professor Schaudinn, unfortunately too late to obtain an answer before his lamented death; but I received an early reply from Dr. Hartmann, of the Hamburg School of Tropical Medicine, which was to the effect that the organism differs from all hitherto known flagellates, so may most conveniently be called the Leishmania-donovani, as suggested by Professor Ross, while as he informed me that this was also the opinion of Dr. Schaudinn, it may safely be adopted.

Such a startling discovery as that just related necessarily needed confirmation before being generally accepted, but this was soon supplied by Assistant Surgeon G. C. Chatterjee, working in my own laboratory, and some three months later independently by S. R. Christophers in Madras (the publication of whose observations was much delayed by the Government regulations applying to him), while several months later still J. Statham, R.A.M.C., and Leishman also confirmed my work in England.

Conditions Affecting the Development of the Flagellate Stage.

In my earlier cultures the amount of development obtained was extremely variable, for although in nearly all of them the earlier stages were seen, yet only about in one in six was the flagellate stage reached, and then usually it was very scantily present as compared with the enormous numbers of slightly developed bodies. This variability and incompleteness of the development pointed to the experimental conditions being still far from the most favourable ones for the extra-corporeal stage of the parasite, and led me to carry out a long series of observations extending over a year, in order to try to ascertain the optimum conditions for its development; this might be expected to furnish a clue to those under which the flagellate forms exist in Nature, and so to the probable mode of infection of the disease it causes. Over one hundred cultures were made before success was obtained, in the course of which a number of negative conclusions were arrived at, which are not without some practical bearing on the problem.

Temperature Limitations.—It was early found that a temperature far below that of the human body is essential to success, from 20° to 22° C. being the optimum one, while I have never got very marked development above 25° C. or 77° F., exposures to higher temperatures than this for but a few minutes causing rapid death and degeneration of all the developing forms—a point of the greatest importance in connexion with the season of the year when the infection of the disease takes place, as pointed out in my last lecture. The minimum temperature below which the development will not take place has not yet been absolutely settled, owing to the short cold season in Calcutta, but as far as my observations go they point to from 15° to 17° C., or about 60° F., as the lower

favourable point, which is in accordance with the seasonal and climatic distribution already given.

Sterility.—Another point of crucial importance is the sterility of the culture tubes, especially as regards micrococci, contamination with bacteria during the frequent examinations of the tubes having been always followed by rapid death and degeneration of these protozoal parasites. Staphylococci exerted the greatest effect in this direction, which affords a possible explanation of the occasional favourable effect on the fever of kala-azar following septic complications already referred to in my last lecture. This necessity for sterility explains why the parasites have never been found in the faeces in those occasional cases in which they are present in the bases of ulcers in the intestines, while it renders this mode of escape from the body being the ordinary source of infection extremely improbable. As I was also unable to obtain any development whatever in even sterile water, this agency, which is probably never sterile in Nature when at a temperature suitable to the development of the parasite, may also be put out of court as the common vehicle of infection, especially as all clinical experience is also against it. Different strengths of salt solution were tried, and only showed that somewhere about that of the blood or slightly higher degrees were most favourable to the process.

Anaërobic Conditions.—An atmosphere of hydrogen or nitrogen gas prevented the development without killing the organism, which might develop well on the cultures being again placed under ordinary atmospherical conditions, once more pointing to the intestinal canal as unfavourable for the process. On the other hand, an atmosphere of oxygen gas did not appear to affect the development.

Acid Medium.—All the negative results just mentioned, taken together with a number of facts regarding the conditions influencing the spread of the disease ascertained during its study in Assam, led me to the conclusion that the mode of the infection must be through some biting insect. As the mosquito seemed to be an unlikely agency on account of the strictness with which the infection appeared to be limited to houses containing cases of the disease, I strongly suspected that pest of Indian life, the homely bedbug, to be the culprit. During some earlier unpublished examinations of the contents of the stomachs of bugs from the beds of plague patients for bacteria I had been struck by the frequency with which the contents were absolutely sterile—a somewhat unexpected result. I therefore tested the reaction of the fluid in the stomachs of these insects after sucking human blood, and found it to be distinctly acid, the secretions of the organ being evidently sufficient to neutralize the natural alkalinity of the imbibed blood. This fact led me to try the addition of a drop or two of weak sterile citric acid solution to the infected citrated human spleen blood, so as to neutralize or faintly acidify the medium, and at

last my patience was rewarded by obtaining a far more abundant and uniformly complete development of active flagellated forms than I had ever seen before in scores of cultures, the rosette-like groups being especially abundant and active. What was most striking and important was the fact that, instead of the vast majority of the organisms showing little or no development (but very few reached the flagellate stage in the previous alkaline blood cultures) in the acidified medium all the organisms appeared to develop uniformly, so that when, about the third day, the flagella began to be seen it was found that the vast majority of the organisms, which were multiplying with extreme rapidity, had already reached this advanced degree, and a day or two later few or none remained in the original small undeveloped stage. It was clear, then, that this acidified sterile fluid blood medium kept at a temperature of about 20° C. to 22° C. was extremely favourable to the growth of the extra-corporeal stage of the organism, and might with a very great degree of probability be relied on to furnish the long-wanted key to the most likely intermediate host of the parasite. All the developmental forms in the diagram have been drawn from one of these acid cultures.

Feeding Experiments.

The success of the acidified blood as a culture medium having now greatly strengthened my suspicion that the bedbug is the carrier of the infection of kala azar, I next tried a variety of methods to induce these insects to swallow infected human blood placed in sterile capsules of different kinds, but without success, as they refused to be tempted to suck the blood. In order to ascertain if the stomachs of these particular insects was likely to prove suitable for the development the plan was next adopted of mixing human spleen blood containing the organisms with about an equal quantity of the fluid contained in the stomachs of these insects after feeding on human blood, in sterile capillary tubes, and I thus also succeeded in obtaining the development of fully-flagellated forms at the suitable temperature, so that it only remained to find similar forms in these insects after feeding on kala-azar subjects to complete the proof that they may actually be the carriers of the infection, as far as it is possible to do so as long as no animal is known which takes it, for it would not be justifiable to try to infect human subjects with such a deadly disease, and hitherto all attempts to inoculate the ordinary laboratory animals or even monkeys have failed. As far as I know the anthropoid apes have not been experimented upon owing to the difficulty and expense of obtaining them, one orang-outang which I got for the purpose having died too soon to enable this point to be settled.

As sufficiently numerous feeding experiments with such insects to be of any value require much time, I spent in Assam all the leave I could obtain last year when the temperature conditions were favourable for this

purpose; but, although I examined blood from the stomachs of over 200 bugs fed on kala-azar patients with low powers in a fresh condition for active flagellate forms, I had met with no success when I had to stop on account of my eyes, and have only been able to find time since to examine a few of the stained slides then made. This failure was disappointing, but the time available for the work was so short that I did not regard the negative result as in any way invalidating my theory; I was therefore much pleased to learn several months later that W. S. Patton, I.M.S., had been placed on special duty to work on similar lines, and still more when it was announced in the *Indian Medical Gazette* that he had obtained some development of the kala-azar parasites in the stomachs of bedbugs, but not in those of mosquitos, ticks (with which S. R. Christophers had previously obtained negative results) or lice. While on a visit to Madras last Christmas holidays Dr. Patton kindly showed me his specimens, which clearly contained the early stages of the development with the appearance of the eosin body, and in one of his drawings a short flagellum was also apparent. They struck me as being very similar to the scanty development I obtained before using acidified media, and gave me the impression that the conditions were not those most favourable to the process; and on inquiry I found that attention had not been paid to the obtaining the most favourable temperature for the development, so I urged him to do as many feeding experiments as possible during the then more favourable cold season, when the optimum temperature could be obtained. The result has fully substantiated my opinion, for within three weeks Patton wrote to me: "I have got the complete cycle of the parasite up to completely developed flagellates"; and added, "There is no shadow of doubt that the bedbug transmits the disease."

Much doubtless remains to be done in this direction in order to ascertain exactly in what form the parasite is again inoculated into the human subject, for the long time during which the infection clings to houses points to the possibility of it being transmitted through the progeny of the first affected bugs, just as occurs in the case of the piroplasma of cattle and dogs; hence that the ovaries and salivary glands should be carefully examined in fed insects for further stages of the parasite. Nevertheless, our knowledge of the life-history of the kala-azar organism is now sufficiently known to enable the facts to be made practical use of in the prophylaxis of the disease, which is the last portion of my subject remaining to be considered.

The Prophylaxis of Kala-azar.

I have already mentioned the partial success of moving infected villages to new sites but a short distance away, which, taken with the strong evidence I collected in 1897 as to the infection being a house one, appeared to me to

afford the most promising basis for preventive measures. Finding also that over a year before I went to Assam Dr. Dodds Price, suspecting the disease to be infectious, had placed 150 out of 200 freshly-imported coolies in newly-built lines of houses, while the remaining 50 had to be accommodated in infected lines for want of room, I got him to work out the results of this measure. It was thus ascertained that although none of the 150 in the new lines had suffered from kala-azar during two years they had been on this badly-infected tea garden, yet no less than 8, or 16 per cent., of those placed in the old lines were already dead of the disease, and that, too, in spite of the fact that the new lines were but 300 yards from the old ones, a distance insufficient to prevent the spread of malaria through the agency of mosquitos.

This very important result obtained by Dr. Price encouraged me to suggest the further step of moving all the healthy people out of infected lines to houses on a new site, no person, however, being taken from an infected hut in consequence of the impossibility at that time of differentiating the early stages of kala-azar from ordinary malarial fever. This plan was carried out by Dr. Price in the case of a coolie line which was so badly infected that no less than 144 out of 240 souls were either actually suffering from kala-azar or had cases in their households, leaving only 96 who could be moved to the new site, 5 of whom were very shortly afterwards sent back on account of their developing fever. A large number of fresh coolies were also drafted into these new lines, so that eighteen months later it contained 416 souls, among whom not a single case of kala azar had occurred, a statement which happily remains true at the present time, ten years after they were occupied.

In marked contrast with this result is the fact that of 60 coolies who refused to move out of the infected lines no less than 20, or one-third, were attacked within the eighteen months, and a year ago they had nearly all been carried off by the disease, although their houses were only 400 yards from the new ones which remained healthy. This experiment was so conclusive that it has since been often repeated with uniformly good results, so that the disease is no longer as dreaded as it used to be by tea planters in the Nowgong district. In slightly-infected lines only the affected households were segregated and their houses burnt, this measure being also of value, although less effective than the former one. It is only in the few remaining old lines that the infection lingers at the present time, and I am glad of this opportunity of saying that Dr. Dodds Price deserves the greatest possible credit for initiating and successfully carrying out these measures, especially as he has been too modest to claim it himself. It is not too much to say that it is now certain that this awful scourge can be robbed of most of its terrors whenever it is possible fully to carry out segregation measures, as on tea estates, while their success has encouraged the application of the same principles in

dealing with the spread in villages, as far as they are practicable in that case.

Measures to Check the Spread of Kala-azar in the Villages.

It was not possible to carry out such complete measures as the above in the infected villages, but the following recommendations of mine proved successful in preventing the spread of the disease into the eastern half of the Brahmaputra Valley, as already described. In the first place, a pamphlet in the vernacular was widely distributed, explaining, in simple language, the manner in which the infection was spread and the precautions necessary to prevent its introduction into unaffected places, and by thus putting the people on their guard against the insidious invasion of the disease they were often enabled to keep it at bay without having to learn the lesson by bitter experience. In the second place, assistance was given by the Government to already infected villages to remove to a new site, the infected persons being, as far as possible, accommodated in a separate place.

It may, then, be fairly claimed that much practical good resulted from my inquiries of 1896-7, both in the prevention of the further spread of the disease up the Assam Valley and also in its being practically stamped out of the Nowgong tea gardens, and it is worthy of note that all this was accomplished before the exact nature of the disease was ascertained by the discovery of the parasite in 1903. Moreover, the success of the measures based on the theory that the disease was essentially a house one is readily accounted for by the bug theory of infection, which has now received such strong experimental support.

The Destruction of Bedbugs as a Prophylactic Measure.

Just a year ago, several months before Dr. Patton's successful feeding experiments, I arranged with Dr. Dodds Price for him to try the effect of repeated attempts to destroy all forms of insect life in the infected houses and those immediately around them in a coolie line in which kala-azar cases continued to arise each cold weather, leaving a second slightly-infected one as a control. The houses were fumigated with burning sulphur, the beds thoroughly washed with strong boiling carbolic lotion, the clothes either boiled in the same solution or destroyed, while the blankets were all burnt as being most likely to harbour bugs, new clothes and blankets being supplied. In the line which was thus treated 6 cases had occurred during the cold season of 1905-6, all in adjoining houses, and the disease seemed to be slowly extending, so that Dr. Price considered this spot to be "a regular hotbed of kala-azar."

I have just received the results of this experiment up to the beginning of February, thus including three-fifths of the cold season, when fresh cases of kala-azar mostly appear, and so far no coolie has been attacked in the disinfected lines of houses. Satisfactory as this result is, it

must be admitted that it is not quite conclusive, because in the control slightly-infected line, which was not disinfected, there have also been no fresh cases of the disease, although this is not altogether surprising, as since last year all the cases in this control line have either died or recovered, leaving no foci in it from which infection was likely to take place, so that, as Dr. Price remarks in his letter, new cases would have been much more likely to have occurred in the disinfected than in the untreated lines.

The result of this effort to destroy bedbugs in the houses infected with kala-azar is, at any rate, most encouraging, and in view of Dr. Patton having now proved that the parasite can develop into the flagellate stage in the stomachs of bedbugs fed on kala azar patients and kept at the right temperature, it may safely be laid down that somewhat similar disinfecting operations to those just mentioned should be carried out in all houses from which kala-azar patients are received, for this measure may be expected to do much towards preventing the disease running through the families of poor Europeans in the way I have described, and the terrible mortality in children in particular may be greatly lessened. In this way it is not too much to hope that as much may be done to reduce the present terrible loss of life due to the sporadic form of kala-azar in Bengal and Madras—at any rate, among Europeans—as has already been accomplished in limiting the spread of the epidemic in Assam, and stamping it out in coolie lines; and thus the knowledge regarding the life-history of the parasite obtained by the investigations of the last four years may supplement and extend the scope of the prophylactic measures previously put into successful operation to stem the progress of the Assam epidemic kala-azar.

I have now completed my task, and although I have necessarily had to dwell a good deal on my own work, especially when treating of the epidemiological and clinical side of the subject, on account of the very exceptional opportunities I have enjoyed of studying these aspects of the question, I have also endeavoured to do full justice to the invaluable work of the numerous observers who have added so much to our knowledge; and in concluding I wish to emphasize the fact that the great advances made during the last few years in our knowledge of the most terrible of all tropical diseases is a pleasing instance of the recent increased interest in tropical affections, leading to combined work in different places by a number of medical men, all, happily, of British nationality.